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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER
LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER

MCKENZIE, THOMAS C

ART UNIT PAPER NUMBER

1624

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/647,234

Applicant(s)

YAMADA ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 July 2005 and 23 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-37 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 30-33 is/are allowed.
- 6) ☒ Claim(s) 21-29 and 34-37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/3 12/3 12/3&3/5.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

S-20

DETAILED ACTION

1. This action is in response to amendments filed on 7/6/05 and 5/23/05. Applicant has canceled claims 1-20. Claims 21-37 are new. The previous claims 3-11 and 13 were indicated as containing allowable subject matter. Claims 21-33 are compound claims. Claim 34 is a compound claim. Claims 35-37 are use claims. The application concerns some pyrido[4,3-b]pyridine and pyrido[2,3-d]pyrimidine compounds, compositions, and uses thereof.

Response to Amendment

2. Applicants' new claims, which specify the substituents on the various groups, overcomes the indefiniteness rejection made in point #2 of the previous office action. Applicants' new use claims, putting the use into the proper format overcomes the indefiniteness and utility rejections made in point #4 of that action. Applicants' exclusion of pyrido[2,3-b]pyridine compounds from the claims overcomes the art rejections over Bolhofer ('456) made in points #6 and #8. This also overcomes the art rejection over Bolhofer (J. Med. Chem.) made in point #7.

3. The declaration by Dr. Omori under 37 CFR 1.132 filed 5/23/05 is sufficient to overcome the rejection of claim 35 based upon lack of enablement. This declaration shows that 21 of the compounds embraced by the present formula (I) are potent inhibitors of the PDE V enzyme. As such, they could be effective treatments of erectile dysfunction.

4. The declaration by Dr. Kikkawa under 37 CFR 1.132 filed 5/23/05 is sufficient to overcome the rejection of claim 35 based upon lack of enablement. This declaration shows that five of the compounds embraced by formula (I) reverse the contraction induced by phenylephrine in corpus cavernosum tissue. According to the On-line Medical dictionary, the corpus cavernosum is "[o]ne of two parallel columns of erectile tissue forming the dorsal part of the body of the penis". It contains blood vessels that have nitrergic nerves that synthesize nitric oxide. The drug Sildenafil selectively inhibits PDE V and allows corpus cavernosum smooth muscle to relax, potentiating erections during sexual stimulation.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-29 and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Formula (I) is missing from claim 21, five formulas are missing from claim 26, and one formula may be missing from claim 27. In the last two lines of claim 27, Applicants use the phrase "a group of the formula:" twice but only have one formula.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating erectile dysfunction, does not reasonably provide enablement for treating pulmonary hypertension or diabetic gastroparesis. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. “The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims”, *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The three main issues are the lack of any correlation between clinical efficacy for pulmonary hypertension or diabetic gastroparesis treatment and PDE V activity, the state of the prior art, and the breadth of the claims.

The state of the clinical arts in PDE V associated diseases is provided by Perry (Current Opinion in Chemical Biology). Perry (Current Opinion in Chemical Biology) states in the first sentence, first complete paragraph, column 2, page 478 that "the role of PDE5 inhibitors in cardiovascular therapy has yet to be clinically established". He reports that the FDA has approved the PDE V inhibitor Viagra (sildenafil) only for the treatment of "male impotence and erectile dysfunction". Corbin (Int J Clin Pract.) states that "inhibitors that are selective for phosphodiesterase-5 (PDE5) represent a promising new class of compounds that are useful for the treatment of erectile dysfunction and perhaps other disorders". "[P]erhaps" is not the standard for disease treatment enablement. Cremers (Herz) states in his abstract, "little is known about other potential beneficial effects of [the PDE V inhibitor] sildenafil". "[S]ildenafil may be a useful adjunct to inhaled iloprost in the management of pulmonary hypertension." "In gastrointestinal disorders, sildenafil also exerts several effects which might be of clinical relevance." Thus, in 2003, two years after Applicants effective filing date, applications of sildenafil to treatment of diseases other than erectile dysfunction were speculative.

The scope of the claims involves all of the thousands of compounds of claim 21 as well as the two claimed diseases. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

8. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.


Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624
(571) 272-0670